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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/961,089	CHIN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-23, drawn to methods of eliminating redundant sequences, which are common between two samples through amplification and sequencing, classified in class 435, subclass 6.

   II. Claims 24-25, drawn to methods of degrading hybrids using S1 nuclease or Exonuclease enzymes, classified in class 435, subclass 183.

2. The inventions are distinct, each from the other because of the following reasons:

A) Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are directed to methods which have different methods, starting materials, and goals. Invention I is directed to methods of eliminating redundant sequences which are common between two samples through amplification and sequencing, whereas Invention II is directed to methods of degrading hybrids using S1 nuclease or Exonuclease enzymes.

3. Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-II require different searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Robert C. Chin on December 20, 2001 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in responding to this Office action. Claims 24-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

5. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Specification

7. The disclosure is objected to because of the following informalities:

A) The specification contains numerous recitations of "(_Ref###)" when referring to cited references. The specification should be amended to only include the correct citation to a reference. For example, in the first paragraph on page 1: "(_Ref488664383Lennon, G.G. (2000) DDT, 5:59-66_Refe48864383)", could be amended to recite, "Lennon, G.G. (2000) DDT, 5:59-66".

B) The disclosure (page 3) is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

C) In claims 1 and 12, the "." should be deleted after the ")", since a period should only come at the end of the claim.

D) In claims 6 and 18, Applicants could amend the claim to recite, "claims 3 and 4,". Additionally, claim 18 improperly depends from claims 3 and 4. Applicants should amend the claim to reflect the correct dependency.

E) The use of the trademark "Amplitaq Gold Polymerase" and "MegaBace DNA Sequencer" has been noted in this application (especially in claims 8, 10, 20, and 23). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-23 over "biomolecular degrading enzymatic reagents", "radiolabeled assay" (claims 1-11) and "fluorescence dye assay" (claims 12-23) because it is not clear as to what is meant by these recitations, and furthermore, the specification fails to define these terms.

B) Claims 1-23 over "the remaining sequences" and "the hybridized complements" because these recitations lack antecedent basis. See MPEP 2173.05(e).

C) Claims 1-23 over "uniquely expressed or over and under expressed in these samples" because it is not clear as to what is meant by "uniquely expressed" and "over and under expressed", what the difference (if any) between "uniquely expressed" or "over and under expressed" is, and how this is material to the claimed invention.

D) Claims 1-23, because the claims do not recite a final process step, which clearly relates back to the preamble.

E) Claims 1-23 are indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims do not logically depend from each other. For example, does step b) generate cDNA from the RNAs of step a)? In addition, in step a), if DNAs are isolated (i.e. not RNAs), it is not clear as to how the method is carried out.

F) Claims 1-23 over "RT-PCR methods and technologies" because it is not clear as to what is meant by this recitation. Applicants could amend the claims to delete "methods and technologies". In addition, Applicants could delete "using" and insert "by".

G) Claims 1-23, because it is not clear as to what "resultant cDNA or RNAs " will exist after the degradation step of d). It appears as if the complete degradation of the cDNAs and RNAs occurs in step d), and therefore, it is not clear as to how the method can be carried out.

H) Claims 1-23, because steps e) through h) are unclear. First, it is unclear that RNAs are amplified directly by PCR. Additionally, it is not clear as to what constitutes "displaying and reading" the resultant cDNAs or RNAs. Finally, it is not clear as to what "unique" cDNAs and RNAs are.

I) Claims 2-4 and 13-15 over "which RNAs and DNAs are isolated using standard prior art methods and technologies" because this claim is redundant, since step a) is already drawn to "isolating". Furthermore, it is not clear as to what is meant by "standard prior art methods and technologies" because the specification does not define this. Applicants could amend claim 2 to recite, "wherein the samples of interest in step a) is selecting from the group consisting of cells, tissues, pathogens, plants and animals.".

J) Claims 3, 4, 14 and 15 over "the samples". Claims 2 (which claims 3 and 4 depend from) and 13 (which claims 14 and 15 depend) are drawn to a method, not to samples. Applicants could amend the claims to recite, "The method of claim 2, where in said samples…", and "The method of claim 13, where in said samples…".

K) Claims 3 and 14 over "little or totally known genetic sequence information" because it is not clear as to what constitutes, "little or totally known genetic sequence information".

L) Claims 4 and 15 over "developmental, change" because it is not clear as to what a "developmental" is. Applicants could amend the claim to recite, "developmental change".

M) Claim 5 over "radioactive labeled" because it is not clear as to what is "radioactive labeled".

N) Claims 7 and 19 over "VII enzyme" because it is not clear as to whether this refers to "Exonuclease VII" or simply an enzyme called "VII enzyme".

O) Claims 9 and 21 over "wherein said displaying...is a electrophoresis gel or capillary electrophoresis" because it is not clear how the displaying "is" an electrophoresis gel or capillary electrophoresis.

P) Claim 10 over "wherein said reading...is a photographic plate" because it is not clear how the reading "is" a photographic plate. In addition, it is not clear as to what a "photographic plate" is, as it is not defined in the specification.

Q) Claims 11 and 23 over "or similar automated sequencers" because it is not clear as to what sequencers are considered to be "similar" to the MegaBace DNA Sequencer.

R) Claim 16 over "fluorescence dyes labled" because it is not clear as to what is "fluorescence dyes labled".

S) Claim 17 over "the fluorescence dyes". Claims 16 (which claim 17 depends from) is drawn to a method, not to fluorescence dyes. Applicants could amend the claims to recite, "The method of claim 6, where in said fluorescence dyes...". Furthermore, it is not clear how dyes absorb and "fluorescence" at two distinct wavelengths. Additionally, it is not clear what is meant by "fluorescence a two distinct fluorescence lifetimes, and fluorescence at two distinct polarizations". These recitations are defined in the specification.

T) Claim 22 over "wherein said reading...is a scanning fluorescence spectrophotometer" because it is not clear how the reading "is" a scanning fluorescence spectrophotometer.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-7, 9-19 and 21-23 rejected under 35 U.S.C. 103(a) as being unpatentable over Zeng (USPN 5,525,471), in view of Burmer et al. (USPN 5,935,788).

Due to the lack of clarity of claims 1-23, these claims have been interpreted as a method of subtractive hybridization.

Zeng teaches a method of subtractive hybridization comprising, isolating RNAs and DNAs, generating cDNA from said isolated RNA by RT-PCR, mixing cDNAs, degrading the hybridized complements using degrading reagents, amplifying resultant cDNAs and sequencing unique cDNAs (see abstract, Fig. 1, col. 2-7).

Additionally, Zeng teaches:

- Samples of interest can be differentiated cells (col. 3) (claims 2-4 and 13-15).
- RT-PCR is carried out using oligo dT primers (col. 7) (claims 5 and 17).
- Degrading agents comprise Exonucleases III and VII (col. 2) (clams 7 and 19).
- Displaying resultant cDNAs or RNAs are carried out using gel electrophoresis (col. 9-10) (claims 9 and 21).
- Resultant RNAs can be read via a photographic plate (col. 10) (claim 10).

Zeng does not teach the cross mixing of complementary cDNAs with RNAs of samples of interest.

However, Burmer teaches a method of subtractive hybridization, wherein RNA can be used as the second nucleic acid in a subtractive hybridization, which would result in a cross mixing of cDNAs with RNAs of samples of interest (col. 4) (claims 6 and 18).

Additionally, Burmer teaches the use of labels in amplification (claims 5 and 17), the use of photographic plates and scanning fluorescence spectrophotometers for detection (claims 10 and 22), and that the nucleic acids can be sequenced using similar automated sequencers (col. 9-10) (claims 11 and 23).

In view of the teachings of Burmer, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Zeng so as to have included RNA as the second nucleic acid to hybridize a cDNA with an RNA sample of interest, in order to have achieved the benefits stated by Burmer of preventing the isolation of intronic genomic sequences (col. 4).

12. Claims 8 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeng (USPN 5,525,471), in view of Burmer et al. (USPN 5,935,788), and in further view of Kozian et al. (USPN6,342,376).

The references above teach the claimed methods, wherein amplification is carried out using Taq polymerase. The references do not teach the use of AmpliTaq Gold Polymerase.

However, Kozian teaches that several polymerases are functional equivalents and can be used interchangeably when used in amplification. Kozian teaches that these polymerases include:

"a DNA polymerase, preferably a DNA-dependent DNA polymerase, with particular preference being given to this DNA polymerase being a temperature-stable DNA polymerase such as Taq polymerase, VENT polymerase, AmpliTaq polymerase or AmpliTaq Gold polymerase" (col.)

In view of the teachings of Kozian, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Zeng and Burmer so

as to have included AmpliTaq Gold Polymerase, instead of Taq polymerase, in order to have achieved and equally effective means of amplification.

Conclusion

13. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
November 13, 2002

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

11/13/02